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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/531,369	03/21/00	WILLIAMSON M	07334-122001

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EXAMINER	
CANELLA K	
ART UNIT	**PAPER NUMBER**
1642	//

DATE MAILED: 03/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/531,369	Williamson
Examiner	**Group Art Unit**
Karen Canella	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3 months* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) *4-20* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4,8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Acknowledgment is made of applicant's election of Group I, claims 1-3, without traverse.

2. Claims 1-20 are pending. Claims 4-20, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-3 are examined on the merits.

Information Disclosure Statement

3. References AQ, AS and AT of the IDS submitted on 3/21/00 are duplicates of references submitted in the IDS of 9/25/00. Lined out reference AR of the IDS submitted on 3/21/00 was not present in the file. Applicant is invited to provide a replacement copy.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1 and 2 are drawn to a method for determining if a test compound modulates the drug-resistance of a cell comprising the identification of compounds which alter the level of expression of MDA-9. Claim 3 is drawn to a method for determining whether a test compound modulates the drug-resistance of a cell comprising selecting test compounds which bind to the MDA-9 protein, determining if the selected test compound alters the drug-resistance in a non-human mammal. The specification teaches that the polynucleotide of SEQ ID NO:1, as clone cohyr002g08, 1 was expressed at higher levels in three doxorubicin resistant cancer cell lines than in the corresponding drug-sensitive cell lines from which the drug-resistant cell lines were derived. SEQ ID NO:1 was subsequently identified as being identical to MDA-9, melanoma differentiation

associated protein 9. The specification then discusses MDA-9 protein as an integral part of drug resistance in tumor cells. The claims are drawn to modulation of drug resistance by the alteration of expression of MDA-9, and modulation of drug resistance by administering a compound which binds to MDA-9 thereby decreasing the putative activity of MDA-9. However, the specification fails to provide objective evidence that decreasing the level or activity of MDA-9 can modulate drug resistance. The specification further fails to demonstrate specific agents which can modify the level of MDA-9 or bind MDA-9 and thus influence drug resistance.

(A)As drawn to MDA-9 as mediating drug resistance

Claims 1-3 are drawn to methods of determining if a test compound modulates the drug resistance in a cell by determining if said test compound alters the level of expression or putative function of MDA-9. It is well know in the art that the expression profiles of a cell line are altered when the cell becomes drug-resistant. However, not all of the proteins expressed at elevated levels in drug-resistant cells versus drug-sensitive cells are part of a drug resistance mechanism. For instance, Bertram et al (Anti-Cancer Drugs, 1998, Vol. 9, pp. 311-317) teach that analysis of gene expression in doxorubicin-resistant cell lines as compared to sensitive parental cell lines revealed the elevated expression of three genes: MAGE3, S100P and CAPL. S100P and CAPL are proteins necessary for calcium metabolism, not drug-resistance. MAGE3 is similarly not part of any molecular transporter or efflux pump mediating drug resistance. Therefore, not all genes isolated by differential screening based on drug resistance are part of the drug resistance mechanism and one cannot assume that the modulation of said genes and proteins could reverse the drug resistant phenotype. Without objective evidence regarding the alteration of drug-resistant phenotype by a compound which modulates the level of expression or activity of MDA-9, one of skill in the art would be subject to undue experimentation, without reasonable expectation of success, in order to practice the claimed methods.

(B)As drawn to compounds which bind to MDA-9 and compounds which alter the expression of MDA-9

Claims 1 and 2 are drawn to methods for identifying compounds which modulate the drug-resistance of a cell by altering the expression of MDA-9. Claim 3 is drawn to a method for

identifying compounds which modulate the drug-resistance of a cell through binding to MDA-9. For the reasons given in paragraph (A) above, the specification is not enabling for a method of modulating drug-resistance in a cell. Further, the specification is not enabling for methods which alter the expression or activity of MDA-9. The specification does not describe in sufficient detail any proteins, peptides or small organic molecules which can bind to MDA-9 and thus alter the putative activity of MDA-9. The specification discusses the potential use of antisense nucleic acids and triple helix technology to decrease the level of mRNA encoding MDA-9. However, beyond the suggestion that the entire polynucleotide sequence encoding MDA-9 can be placed in a vector in anti-sense orientation, no further guidance is given in choosing antisense or triple helix forming oligos to inhibit the expression of MDA-9. It is recognized in the art that the development of clinically useful antisense strategies for disease therapy is fraught with difficulties, even when the nucleic acid sequence for the target protein is known. Antisense nucleic acids, such as antisense cDNA or antisense exons, which are large and highly charged often interact with a wide variety of untargeted cellular components causing undesirable "non-antisense effects" (A.Branch, Hepatology, 1996, Vol. 24, pp. 1517-1529). Antisense nucleic acids must be optimized for use in patients. Furthermore, with regard to triple helix forming oligomers, neither the specification or any art of record contains teachings regarding potential sites in the MDA-9 polynucleotide that would be amenable to hybridization of a triple-helix forming oligo. In order to use anti-sense or triple helix technology for reversal of the drug-resistance phenotype, careful consideration must be made with respect to the target nucleotide sequence within the gene of interest, the choice of backbone modifications for the oligonucleotide, and the presence of special sequence motifs which predispose the oligonucleotide to undesirable non-antisense effects (Broaddus et al, Methods in Enzymology, 2000, Vol. 314, pp. 121-135). The published data indicates that only a small percentage of the antisense oligonucleotides which are tested in vitro are actually effective in the reduction of the target mRNA, and that the ability of the anti-sense oligonucleotides to bind to a target mRNA cannot be predicted due to the structure and conformation assumed by individual mRNA specie (Broaddus et al, pg. 122). Further, even if the specific structure and conformation of a particular mRNA could be adequately predicted as an

isolated molecule in a protein-free environment, it would not anticipate the accessible sites for the anti-sense oligonucleotide in vivo, wherein proteins are available to bind to the mRNA thus obscuring the oligonucleotide binding sites and potentially altering the conformation of the target mRNA. Broaddus et al teaches that a highly empirical approach to the testing of candidate anti-sense oligonucleotides is critical for the establishment of an antisense oligonucleotide as a therapeutic agent for the treatment of patients. This requirement has not been met by the instant specification, therefore, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
February 25, 2001

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